

What is claimed is:

- Sub A'
1. A method of enhancing an endogenous immune response-mediated specific elimination of a population of pathogenic cells in a host animal harboring said population wherein the members of said cell population have an accessible binding site for a ligand, said method comprising the step of
5 administering to said host
a ligand-immunogen conjugate composition comprising a complex of the ligand and an immunogen wherein said immunogen is known to be recognized by an endogenous or an exogenous antibody in the host or is known to be
10 recognized directly by an immune cell in the host; and
at least one additional composition comprising a therapeutic factor, said factor being selected from the group consisting of a cell killing agent, a tumor penetration enhancer, a chemotherapeutic agent, an antimicrobial agent, a
15 cytotoxic immune cell, and a compound capable of stimulating an endogenous immune response wherein the compound does not bind to the ligand-immunogen conjugate.
2. The method of claim 1 wherein the population of pathogenic cells is a cancer cell population.
3. The method of claim 2 wherein the cancer cell population is
20 tumorigenic.
4. The method of claim 1 wherein the population of pathogenic cells is an exogenous pathogen or an endogenous cell population harboring exogenous pathogens.
5. The method of claim 4 wherein the exogenous pathogen is selected
25 from the group consisting of bacteria, fungi, viruses, mycoplasma, and parasites.
6. The method of claim 1 wherein the ligand is a vitamin capable of specifically binding to a cell membrane receptor.
7. The method of claim 6 wherein the ligand is selected from the group
30 consisting of folic acid and other folate receptor-binding ligands.
8. The method of claim 1 wherein the ligand is chemically complexed to the immunogen through bonding comprising covalent, ionic, or hydrogen bonding.

9. The method of claim 8 wherein the ligand is a folic acid analog having a glutamyl moiety covalently linked to the immunogen only via the glutamyl γ -carboxyl moiety of the ligand.

10. The method of claim 8 wherein the ligand is a folic acid analog having a 5 glutamyl moiety covalently linked to the immunogen only via the glutamyl α -carboxyl moiety of the ligand.

11. The method of claim 9 wherein the covalent linkage between the immunogen and the ligand is by direct covalent bonding to the immunogen or by covalent bonding through a divalent linker.

10 12. The method of claim 10 wherein the covalent linkage between the immunogen and the ligand is by direct covalent bonding to the immunogen or by covalent bonding through a divalent linker.

15 13. The method of claim 1 wherein the ligand is a small organic molecule capable of binding to a receptor and wherein said receptor is preferentially expressed, uniquely expressed or overexpressed on the surface of said population of pathogenic cells.

14. The method of claim 12 wherein the small organic molecule is an antimicrobial drug.

15. The method of claim 1 wherein the ligand is a β -lactam antibiotic.

20 16. The method of claim 1 wherein the ligand binding site is an antigen preferentially expressed, uniquely expressed or overexpressed on metastatic cancer cells.

17. The method of claim 15 wherein the ligand binding site is EphA2.

18. The method of claim 1 wherein the immunogen is an organic molecule 25 having a molecular weight less than 20,000 daltons.

19. The method of claim 17 wherein the organic molecule is fluorescein or dinitrophenyl.

20. The method of claim 1 wherein the immunogen is an α -galactosyl group.

30 21. The method of claim 1 wherein the antibody is exogenous to said host and is co-administered with said conjugate composition.

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22. The method of claim 1 wherein the therapeutic factor comprises a cytokine.
23. The method of claim 21 wherein the therapeutic factor comprises IL-2, IL-12, IL-15, or combinations thereof.
- 5 24. The method of claim 21 wherein the therapeutic factor comprises IL-2, IL-12, IL-15, or combinations thereof, in combination with IFN- α or IFN- γ .
25. The method of claim 21 wherein the therapeutic factor comprises IL-2, IL-12, IL-15, or combinations thereof, in combination with IFN- α or IFN- γ , or a combination thereof, and GM-CSF.
- 10 26. The method of claim 21 wherein the therapeutic factor comprises at least one NK cell or T cell stimulant.
27. The method of claim 1 wherein the ligand-immunogen conjugate composition is administered in multiple injections.
- 15 28. The method of claim 1 wherein the host animal had been previously exposed naturally to the immunogen so that the host animal has a preexisting immunity to said immunogen evidenced by the presence of endogenous antibodies to the immunogen.
29. The method of claim 1 wherein the host animal had been previously exposed to the immunogen by a non-natural process resulting in priming of the host animal's immune response to said immunogen.
- 20 30. The method of claim 28 wherein the non-natural process resulting in priming of the animal's immune response is vaccination.
31. The method of claim 28 wherein the non-natural process resulting in priming of the immune response is active immunization.
- 25 32. The method of claim 1 wherein the endogenous immune response comprises a humoral immune response.
33. The method of claim 31 wherein the humoral response is an acquired immune response.
34. The method of claim 31 wherein the humoral response is an innate immune response.
- 30 35. The method of claim 32 wherein the acquired response is induced by administering into the host animal a vaccine composition.

36. The method of claim 1 wherein the endogenous immune response comprises a cell-mediated immune response.

37. The method of claim 1 wherein the endogenous immune response comprises a humoral and a cell-mediated immune response.

5 38. A method of enhancing an endogenous immune response-mediated specific elimination of a population of pathogenic cells in a host animal harboring said population wherein said population expresses a binding site for a ligand, said method comprising the steps of

10 administering to the host a composition comprising a complex of said ligand and an immunogen;

 administering to the host antibodies directed against the immunogen;
and

15 administering to said host at least one additional therapeutic factor, said factor being selected from the group consisting of a cell killing agent, a tumor penetration enhancer, a chemotherapeutic agent, an antimicrobial agent, a cytotoxic immune cell, and a stimulant of an endogenous immune response that does not bind to the ligand-immunogen complex.

20 39. A method of enhancing an endogenous immune response-mediated specific elimination of a population of pathogenic cells in a host animal harboring said population wherein said population preferentially expresses, uniquely expresses, or overexpresses a folic acid receptor, said method comprising the step of

 administering to said host

25 a composition comprising a covalently linked conjugate of an immunogen wherein the immunogen is known to be recognized by an endogenous or exogenous antibody in the host or is known to be recognized directly by an immune cell in the host; and

 a ligand comprising folic acid or a folic acid analogue having a glutamyl group wherein the covalent linkage to the immunogen is only through the γ -carboxy group of the glutamyl group.

30 40. A method of enhancing an endogenous immune response-mediated specific elimination of a population of pathogenic cells in a host animal harboring said population wherein said population preferentially expresses, uniquely expresses, or

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overexpresses a binding site for a folic acid receptor, said method comprising the step of

administering to said host

a composition comprising a covalently linked conjugate of an

5 immunogen wherein the immunogen is known to be recognized by an endogenous or exogenous antibody in the host or is known to be recognized directly by an immune cell in the host; and

10 a ligand comprising folic acid or a folic acid analogue having a glutamyl group wherein the covalent linkage to the immunogen is only through the α -carboxy group of the glutamyl group.

41. A method of enhancing an endogenous immune response-mediated specific elimination of a population of pathogenic cells in a host animal harboring said population wherein said population preferentially expresses, uniquely expresses, or overexpresses a binding site for a folic acid receptor, said method comprising the steps 15 of

administering to said host

a composition comprising a covalently linked conjugate of an immunogen wherein the immunogen is known to be recognized by an endogenous or exogenous antibody in the host or is known to be recognized directly by an immune

20 cell in the host;

a ligand comprising folic acid or a folic acid analogue having a glutamyl group wherein the covalent linkage is only through the γ -carboxy group of the glutamyl group; and

25 at least one additional composition comprising a therapeutic factor, said factor being selected from the group consisting of a cell killing agent, a tumor penetration enhancer, a chemotherapeutic agent, an antimicrobial agent, a cytotoxic immune cell, and a compound capable of stimulating an endogenous immune response wherein the compound does not bind to the ligand-immunogen conjugate.

42. A method of enhancing an endogenous immune response-mediated specific elimination of a population of pathogenic cells in a host animal harboring said population wherein said population preferentially expresses, uniquely expresses, or overexpresses a folic acid receptor, said method comprising the step of

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- administering to said host
a composition comprising a covalently linked conjugate of an immunogen wherein the immunogen is known to be recognized by an endogenous or exogenous antibody in the host or is known to be recognized directly by an immune cell in the host;
- 5 a ligand comprising folic acid or a folic acid analogue having a glutamyl group wherein the covalent linkage is only through the α -carboxy group of the glutamyl group; and
at least one additional composition comprising a therapeutic factor, said factor being selected from the group consisting of a cell killing agent, a tumor penetration enhancer, a chemotherapeutic agent, an antimicrobial agent, a cytotoxic immune cell, and a compound capable of stimulating an endogenous immune response wherein the compound does not bind to the ligand-immunogen conjugate.
- 10 43. A pharmaceutical composition comprising therapeutically effective amounts of a ligand-immunogen conjugate capable of specific binding to a population of pathogenic cells in a host animal for specific elimination of said cells by an acquired or innate immune response, co-administered antibodies, or directly by an immune cell in the host, a therapeutic factor selected from the group consisting of a cell killing agent, a tumor penetration enhancer, a chemotherapeutic agent, an antimicrobial agent, and a compound capable of stimulating an endogenous immune response wherein the compound does not bind to the ligand-immunogen conjugate, and a pharmaceutically acceptable carrier therefor.
- 15 44. The pharmaceutical composition of claim 42 in a parenteral prolonged release dosage form.
- 20 45. The pharmaceutical composition of claim 42 wherein the therapeutic factor is an immune stimulant.
- 25 46. The pharmaceutical composition of claim 44 wherein the immune stimulant comprises a compound selected from the group consisting of IL-2, IL-12, IL-15, IFN- α , IFN- γ , and GM-CSF, or combinations thereof.
- Sub A4*
- ADD A5*